REMARKS

Applicant respectfully requests reconsideration and allowance of all pending claims.

I. Status of the Claims

Claims 1 and 3-25 remain pending in this application.

II. The Office has Failed to Establish a Prima Facie Case of Obviousness of the Pending Claims over U.S. Patent No. 4,317,903.

The Office once again has rejected the pending claims as obvious in view of U.S. Patent No. 4,317,903 (Hofstetter). In response thereto, Applicant initially reiterates the arguments previously submitted (see, e.g., Applicant's Response to Final Office Action submitted on September 25, 2008). However, in the interests of brevity, those arguments will not be repeated here.

Applicant additional submits that the Office has failed to establish a prima facie case of obviousness, because the Office has (1) failed to establish that the claimed process is a mere substitution of one known element for another known in the art, and (2) failed to establish that the results of the substitution proposed by the Office would be predictable.

A. The Claimed Subject Matter and Hofstetter

Independent claim 1 is directed to an industrial process for recovering pure **fentanyl** from an impure preparation comprising fentanyl containing phenethyl-piperaniline. The process includes subjecting the impure preparation to reverse-phase high performance preparative liquid column chromatography and recovering pure

fentanyl. The pure fentanyl comprises less than about 0.010 weight percent phenethylpiperaniline. The loading ratio of column media to fentanyl loaded onto the column is in the range of from about 50 to about 150.

Independent claim 24 is directed to a process for purifying an impure preparation of **fentanyl** containing phenethylpiperaniline. The process comprises packing a chromatographic column with a chromatographic packing material and passing an aqueous, acidified solution of impure fentanyl through the column at a loading ratio of from about 50 to about 150. The column is eluted with an aqueous solution of an organic solvent to produce an eluate containing fentanyl and less than about 0.010 weight percent phenethylpiperaniline.

As noted in the present application (see, e.g., paragraph [0015]), Applicant discovered the claimed process can be employed, for example, using a series of collected fractions, which may be partially recycled, to obtain a highly purified fentanyl in a high yield. Specifically, fentanyl is produced with phenethylpiperaniline impurity levels less than 0.010 weight percent in the purified product. Furthermore, Applicant discovered the present process is particularly advantageous as compared, for example, to analytical HPLC, which would require a loading ratio significantly higher than the range recited here (see, e.g., paragraph [0029]).

In contrast to the claimed subject matter, Hofstetter discloses methods of using a reverse-phase high performance preparative liquid chromatography to obtain a highly pure preparation of the antibiotic **lincomycin** hydrochloride. The methods generally comprise a number of steps, including: (a) dissolving approximately 450 grams of the starting material (i.e., impure preparation of lincomycin A and lincomycin B) per liter of 30% aqueous methanol; (b) applying the solution to a chromatography column filled with 18 grams of C18 bonded phase silica gel per gram of starting material; (c) stripping the remaining lincomycin from the column with 1 bed volume of methanol; (d) concentrating the lincomycin-rich eluate to dryness; (e) crystallizing the lincomycin according to standard crystallization procedure; (f) re-chromatographing the lincomycin B-rich fraction according to the above procedure; (g) concentrating the eluate containing

greater than 98% lincomycin B to dryness; and (h) re-dissolving the solids in 3 milliliters of methanol per gram of lincomycin B solids at 40°C and adjusting the pH with concentrated hydrochloric acid to 1.5. Notably, Hofstetter states that the weight ratio recited in step (b) is "near optimum"; that is, Hofstetter states that the weight ratio of silica gel (i.e., the column media) to lincomycin is "near optimum" at 18:1.

The Office argues that one of ordinary skill in the art would arrive at the claimed invention "by routine optimization of existing processes of Hofstetter, by altering by mere substitution of one element for another known in the art." For the reasons set forth in detail below, Applicant respectfully disagrees.

B. The Office has not established that the claimed process is a mere substitution of one known element for another known element in the art, and that the results of the substitution would be predictable.

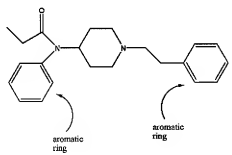
In order to reject the claims as a mere substitution of one known element for another known element in the art, the Office must establish: (1) that the prior art contained a method which differed from the claimed method by the substitution of some components; (2) that the substituted components and their functions were known in the art; (3) that one of ordinary skill could have substituted one known element for another and that the results of the substitution would have been predictable; and, (4) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness. (See, e.g., MPEP §2143(B).)

Applicant submits the Office has failed to establish that one of ordinary skill in the art would have substituted one known element for another, namely (a) purification of fentanyl rather than lincomycin in the process of Hofstetter, (b) purification to less than about 0.010 weight percent of the impurity of concern or interest, and (c) use of a loading ratio of column media to the purified compound from about 50 to about 150 rather, than from 18:1 as in the process of Hofstetter. Further, the Office has failed to

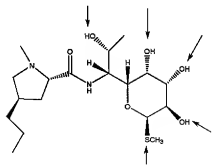
establish that the results of the substitution would have been predictable. More specifically, Applicant submits:

(i) Fentanyl and Lincomycin **are not interchangeable**. It is clearly a central premise in the Office's repeated rejection in view of Hofstetter that lincomycin and fentanyl are so structurally similar as to have "similar chromatographic properties." (See the Office action at the bridging sentence on pages 3 and 4. See also page 4, second full paragraph, wherein the Office states "One skilled in the art . . . of purification of fentanyl would be motivated to modify the process of Hofstetter for purification of fentanyl because Hofstetter teaches the conditions necessary of [sic] purification of a similar compound with similar chromatographic properties.")

Applicant respectfully submits that the Office's position here is **simply incorrect**. As the structures illustrated below indicated, fentanyl has two aromatic rings (denoted by arrows), while lincomycin has none. In addition, lincomycin has four hydroxyl groups and a methyl-sulfur group (denoted by arrows), while fentanyl has none. Finally, the molecular weight and stereochemistry of lincomycin is distinctly different than fentanyl (the molecular weight is 20% greater than that of fentanyl, and lincomycin has rings and susbstituents thereon that have stereochemical configurations that are very different from the planar aromatic rings of fentanyl).



Fentanyl



Lincomycin

In short, **these are simply not similar compounds.** The noted differences in fentanyl and lincomycin would clearly have an effect on how these molecules would interact with the packing in the chromatography column, as well as the solvent system used to elute them from the column. These structural differences are significant, and therefore these molecules **would not have similar chromatographic properties**. As a result, the substitution of fentanyl for lincomycin **is not a matter of routine optimization and mere substitution**, as the Office suggests.

(ii) Furthermore, it is to be noted that the processes of the claimed invention yield a purified fentanyl composition with less than about 0.010 weight percent of phenethylpiperaniline. The Office has provided **no articulation or reasoning** as to why one of ordinary skill in the art would consider that this result would be predictable, in view of the disclosure of Hofstetter. Applicant submits that if one of ordinary skill in the art merely substituted fentanyl into the process of Hofstetter, a purified fentanyl composition with less than about 0.010 weight percent phenethylpiperaniline would not be achieved, due to the differences noted above, and/or due to the 18:1 weight ratio of column media used by Hofstetter.

III. Applicant is Not Required to Respond to the Office's General Remarks Relating to Additional Prior Art References

On page 8 of the Office action, the Office makes reference to "additional references listed in the Office action" and to the "editorial review" of "HPLC: Practical and Industrial Applications by Joel Swadesh" found utilizing GOOGLE. Applicant respectfully points out that the pending claims have not been rejected over these references in the present Office action, or in any previous Office action. Furthermore,

where a reference is relied on to support a rejection, whether or not in a minor capacity, that reference should be **positively included in the statement of the rejection**. (See, e.g., *In re* Hoch, 428 F.2d 1341, 1342 n.3 166 USPQ 406, 407 n. 3 (CCPA 1970); MPEP §706.02(j).) Accordingly, Applicant cannot properly comment on these references, as the Office has not complied with the requirements of MPEP §706.02(j) by setting forth: (A) what the relevant teachings of the art are (preferably **with reference to the relevant column or page numbers**), (B) the differences between the claims and the references, (C) what modifications are necessary to arrive at the claimed invention, and (D) any explanation as to why the claimed invention would be obvious over the cited art.

Furthermore, Applicant objects to the use of an "editorial review" found on GOOGLE (i.e., "HPLC: Practical and Industrial Applications by Joel Swadesh.") Applicant questions the propriety of substituting examination of the reference by the Patent Office with an editorial review of the reference (potentially found on Amazon.com) made by an anonymous source. For example, was the author of the review a person of ordinary skill in the art? Does the review accurately reflect the reference teachings? When did the editorial review publish, and is the editorial review itself being cited as prior art (See MPEP §706.02: "An abstract can have a different effective publication date than the full text document.")?

Applicant invites the Office to formally reject the claims over the cited references if the Office believes the claims are not patentable over them. It is important for the Office to properly communicate the basis for a rejection so that the issues can be identified early and the Applicant can be given fair opportunity to reply. (See, e.g., MPEP §706.02(j).)

Regardless of the above deficiencies, Applicant submits, for the reasons set forth in detail above, that the references do not set forth that the claimed invention is an "optimization of routine methods", as suggested on page 8 of the Office action.

IV. The Office has Failed to Fully Consider the Declaration of Enrico Anthony Antonini

Applicant, the sole inventor of the present application, submitted a declaration on September 10, 2008 in response to the Final Office action dated July 17, 2008 attesting to the patentability of the pending claims. In response to the Declaration, the Office merely states that "the cited prior art is only an Example of methods of the hplc purification technology in the chemical art at the time of the instant application." Applicant reminds the Office that there is **only one outstanding rejection of the claims**, the rejection of claims 1 and 3-25 over **a single reference**, Hofstetter. If the Office wishes to make further rejections, Applicant requests that those rejections be made of record so Applicant may properly respond to them.

As the Applicant has timely submitted objective evidence of patentability of the claims, the Office must consider the evidence. If the Office is of the opinion that the evidence is insufficient to overcome the rejection, **the Office must specifically explain why the evidence is insufficient**. General statements such as "the declaration lacks technical validity" or "the evidence is not commensurate with the scope of the claims", without an explanation supporting such findings, are simply insufficient. (See, e.g., MPEP §716.01.)

V. The Office has Failed to Consider the Patentability of the Dependent Claims

The Office has failed to address the patentability of the dependent claims and the limitations recited therein. Specifically, regarding dependent claim 25, the Office has not established obviousness of a process wherein the eluate is divided into four cuts and the first cut is discarded, the second cut is combined with a fourth cut wherein the aqueous solution of organic solvent is reduced and then recycled through the column and a third cut contains less than about 0.010 percent phenethylpiperaniline. Hofstetter

fails to disclose or suggest such a process and the Office has failed to articulate how or why the skilled artisan would arrive at such a process.

VI. Double Patenting Rejection

As acknowledged by the Office, Applicant respectfully reserves the right to address the merits of this rejection as appropriate, if the listed applications issue as patents before the application at hand.

CONCLUSION

In view of the foregoing, Applicant respectfully requests favorable reconsideration and allowance of all pending claims.

The Commissioner is hereby authorized to charge Deposit Account 13-1160 for any fees due for the submission of this Response to Office Action.

Respectfully submitted,

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